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Review

The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis

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ABSTRACT

Introduction: The use of cannabis or cannabinoids to treat medical conditions and/or alleviate symptoms is increasingly common. However, the impact of this use on patient reported outcomes, such as health-related quality of life (HRQoL), remains unclear.
Methods: We conducted a systematic review and meta-analysis, employing guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We categorized studies based on design, targeted disease condition, and type of cannabis or cannabinoid used. We scored studies based on quality and risk of bias. After eliminating some studies because of poor quality or insufficient data, we conducted meta-analyses of remaining studies based on design.
Results: Twenty studies met our pre-defined selection criteria. Eleven studies were randomized controlled trials (RCTs; 2322 participants); the remaining studies were of cohort and cross-sectional design. Studies of cannabinoids were mostly RCTs of higher design quality than studies of cannabis, which utilized smaller self-selected samples in observational studies. Although we did not uncover a significant association between cannabis and cannabinoids for medical conditions and HRQoL, some patients who used them to treat pain, multiple sclerosis, and inflammatory bower disorders have reported small improvements in HRQoL, whereas some HIV patients have reported reduced HRQoL.
Conclusion: The relationship between HRQoL and the use of cannabis or cannabinoids for medical conditions is inconclusive. Some patient populations report improvements whereas others report reductions in HRQoL. In order to inform users, practitioners, and policymakers more clearly, future studies should adhere to stricter research quality guidelines and more clearly report patient outcomes.
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1. Introduction

The use of cannabis and cannabinoids for medical conditions has become more widespread in the U.S and around the world (Hill, 2015). Access to cannabis for medical use has steadily increased since California passed the Compassionate Use Act in 1996. In the following years there has been progressive deregulation of cannabis prohibition across the country. Driven by voter initiatives, a growing number of states have passed laws permitting use of cannabis for medical conditions, decriminalizing recreational cannabis use, or completely legalizing cannabis use for adults. These events have led to diminished perceptions of risk, increased availability and reduced costs, factors that may contribute to increased use in states with medical marijuana laws (Cerda et al., 2012; Schuermeyer et al., 2014). In 2012, two million individuals, or nearly five percent of the population, in California reported use of cannabis for medical reasons (Ryan-Ibarra et al., 2015). This number does not take into account the individuals who use cannabis, the most commonly-used illicit drug, recreationally (Haberstick et al., 2014). Dronabinol (Marinol) is currently the only FDA-approved cannabinoid in the United States and is only indicated for chemotherapy-induced nausea and vomiting (CINV) and anorexia associated with weight loss in patients with the acquired immunodeficiency syndrome (Kramer, 2015).

There is growing evidence that cannabis and cannabinoids are efficacious for several conditions, such as chronic pain, spasticity, and nausea and vomiting associated with chemotherapy. However, effect sizes are typically small, the quality of evidence is moderate to low, and there is no condition for which either cannabis or cannabinoids have been established as first line agents (Whiting et al., 2015). At the same time, many cannabis users report sub-

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jective benefit of cannabis for conditions for which there is not yet compelling evidence (Reinarman et al., 2011). Barriers to cannabis research have been well documented, and may help to explain some of the disparities between subjective reports and objective findings. However, some controlled studies also reveal discordance between objective clinical response and subjective perception of benefit (Stith and Vigil, 2016; Storr et al., 2014). Given the well characterized ability of cannabis to cause mild euphoria, one pressing question is whether the subjective perceptions of cannabis benefits translate into meaningful and persisting changes in subjective well-being. The best established measures of wellbeing among persons with health conditions are measures of health-related quality of life (HRQoL). HRQoL is a multi-dimensional, patient-reported outcome, that measures subjective sense of wellbeing across multiple domains, including physical, mental, emotional and social functioning.

To understand the impact of cannabis and cannabinoids used for medical conditions on the individuals who utilize them, we conducted a systematic review and meta-analysis of studies evaluating the relationship between cannabis and cannabinoids used for medical conditions and HRQoL. Specifically, we sought to understand whether different forms of cannabis and cannabinoids differentially impact HRQoL, if type of condition/diseases being treated is associated with the impact on HRQoL, and if study design impacted the observed associations between cannabis and cannabinoids use and HRQoL.

2. Methods

We followed the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Liberati et al., 2009; Moher et al., 2009).

2.1. Search strategy

Literature was systematically collected using the following databases: Pubmed, CINAHL, PsycInfo, Cochrane Library of Controlled Trials and Cochrane Library of Systematic Reviews, with inclusion through 2015. We conducted searches using extensive keyword queries, which included: (1) Quality of life terms separated by OR: Quality of life Interviews; Quality of life Index; Global assessment of functioning; SF-36; SF-12; Quality of Life Inventory; WHO Quality of Life Scale; Spitzer Quality of Life Index; self-efficacy; self-autonomy; self-determination; functional status; occupational status; social adjustment; behavior change; behavior modification; quality of life enjoyment and satisfaction; self-concept; self-assessment; self-care; life activities; questionnaire, (2) Cannabis and cannabinoids terms separated by OR: cannabis; marijuana; smoking marijuana; plants; hemp cannabis sativa; sativex; nabilone; cannabinoids; hashish; dronabinol; medical marijuana; bhanga; functional improvement; psychological function; cannabis; quality of life; self-efficacy; self-care; cannabinoids; marijuana; social adjustment; cannabis abuse; marijuana addiction; cannabis use disorders; cannabis abuse; cannabis dependence; cannabis addiction and QoL.

In order to capture all articles that assess HRQoL, we included studies that used the more general keywords “Quality of Life” or “QoL” in the abstract. Next, we searched reference lists from these articles for additional studies of cannabis and cannabinoids that did not appear in the above search.

2.2. Study selection

We manually evaluated the abstracts of all of these studies using the following criteria for inclusion: (1) articles in English or English translation; (2) publication in a peer-reviewed journal; (3) studies that focused on cannabis or cannabinoids; (4) studies that measured HRQoL using a generic or disease-specific multi-item questionnaire; and (5) studies that reported an outcome related to either global or domain-specific HRQoL.

Two reviewers then independently conducted a focused review of the full article text and reached a consensus based on each article’s relevance to this review. A consensus was reached between the two reviewers without exception. We excluded articles if they were poster/presentation synopses, did not relate HRQoL results to cannabis or cannabinoids use, or did not utilize a common validated generic or disease-specific HRQoL scale. Additionally, we excluded articles about participants who used cannabis recreationally, or for no stated medical purpose.

2.3. Study quality and risk of bias

We assessed study bias through analysis of which variables related to cannabis and cannabinoids use, the specific studies held constant, and also by reviewing the strengths and weakness of each study. The studies were assessed for overall quality, risk of bias, sample size, patient selection, interventions, group comparison, outcome measures, and statistical analysis, using study quality criteria adapted from Cochrane Database of Systematic Reviews (Higgins et al., 2011; Higgins et al., 2008).

2.4. Statistical analyses and effects size calculations

We extracted data related to study design, population, and outcomes regarding HRQoL or clinical results. Out of 20 studies collected during our review process, only 11 reported both means and measures of variability (either standard deviations or confidence intervals), so only results from these studies are reported in this meta-analysis. For each study, we utilized either the measure’s index score (from the EQ-5D), or the physical health (PCS) and mental health (MCS) composite scores (from the QLQ-C30, MOS-QoL/SF-36, or MSQOL-54). For two studies(Bestard and Toth, 2011; Svendsen et al., 2004), we calculated PCS and MCS from the available MOS-QoL/SF-36 scale scores, and substituted these in lieu of the reported index scores, using the algorithms created by the developers of the SF-36 (Ware et al., 1994).

We calculated effect sizes separately for index scores and subscale scores on each HRQoL measure implemented across studies. We also calculated effect sizes separately for studies examining changes within patients over time, or differences observed between patients using cannabis and control groups. Typically, an effect size is calculated as the observed change divided by the standard deviation. For between groups effects, we utilized the point-biserial correlation, which weighs the typical effect size calculation by the relative proportions of individuals in both control and intervention samples (Cohen, 1988). This measure of effect size allows us to compare differences in HRQoL changes following the intervention period. To calculate within subjects effects, we utilized Hedges’ *d*, which adjusts the effect size calculation for smaller samples, as was the case with many of the studies in this meta-analysis (Hedges and Vevea, 1998). This measure of effect size captures the changes observed in patients who used cannabis during one of the studies examined herein.

If data were not available in published studies, we contacted the study authors for additional data. Only two authors from the nine studies with incomplete data were able and willing to provide this information for this meta-analysis. If a study included patient outcome reports at multiple time points, we entered this as though they were separate studies. Because the number of studies is low, and these studies appeared heterogeneous with regard to patient

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